II. REMARKS

Claims 1-28 are pending in the subject application. Claims 24 to 28 are withdrawn from consideration as a result of a requirement for restriction. Claims 1 to 23 stand rejected. By this Amendment and Response, claims 1, 2, 5, 8, 11, 12, 13, 16, 17, 18, 22 and 23 have been amended. New claim 29 has been added. Support for the amendments to the claims can be found throughout the specification, and in particular, page 3, lines 12 to 18; page 3, line 22 to page 4, line 12 and page 32, lines 1 though 28. An issue of new matter is not raised by these amendments and entry thereof is respectfully requested. Amended claims 1 to 23 and 29 are currently under examination.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached page is captioned "Version with markings to show changes made".

In view of the preceding amendments and remarks that follow, withdrawal of the requirement for restriction, objections and rejections of the application are respectfully requested.

Applicant's undersigned attorney would like to thank Examiner Nguyen for the courtesy of the January 23, 2002 telephonic interview. The interview was helpful to a complete understanding of the issues set forth in the outstanding Office Action.

Requirement For Restriction Under 35 U.S.C. § 121

The Office noted that Applicant's election with traverse of Group 1 (claims 1-19), in the response filed May 21, 2001 is acknowledged. The Office also stated that Applicant's traversal is found persuasive to the extent that the claims of Group I and claims 20-23 be examined together. The traversal was made final. Accordingly, claims 24 to 28 are withdrawn from examination. However, Applicant retains the right to petition the requirement for restriction.

35 U.S.C. § 112, Second Paragraph

Claims 1-23 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 1, 2 and claims dependent therefrom are allegedly indefinite for the recitation of "range of 1:1 to 1:2" because it is not apparent as to what is exactly the criteria to identity the ratio of "1:1 to :1:2"

Claim 11 is allegedly indefinite for the recitation of a non-proper Markush group. The recitation of "composed of cholesterol 10-60%, ... and....or....,.... and PEG-DSPE" renders the metes and bounds vague and indefinite.

Claim 23 is allegedly indefinite for the recitation of "the cell membrane of a tumor" because while a tumor cell does have a cell membrane, a tumor *per se* consists of a collection of tumor cells, each of which has its own membrane and because the claim refers the method of claim 7, which is directed to a product by process.

Claims 11 and 12 stand rejected for the recitation of percent of a number wherein it is not apparent as to what is exactly the element, *e.g,* weight, volume, the percentage represents.

Claims 16 and 17 are objected to because the claim lacks an article -- A -- at the beginning of the claims so as to conform with standard U.S. practice.

Without conceding the correctness of the Office's position and to advance prosecution and allowance, the claims have been amended in a sincere effort to remove the grounds for rejection. Claims 5 and 18 have been amended to conform to amended claims 1 and 2. The amendment of the claims are not intended to be a disclaimer or dedication to the public of the subject matter of the originally filed. Applicant retains the right to file the same or similar claims in an application claiming the benefit of the subject application.

In view of these amendments, reconsideration and withdrawal of the rejections are respectively requested. proper. Reconsideration and removal of the rejection is respectfully requested.

35 U.S.C. § 103

Claims 1-4, 7-21 and 23 stand rejected under 35 USC 103(a) as allegedly unpatentable over Szoka (U.S. Pat. No. 5,567,434 ("Szoka")) taken with Perez-Soler et al. ("Perez-Soler et al.") and Abra et al. (U.S. Pat. No. 6,126,966 ("'Abra et al.").

The Office alleged that Szoka teaches a cancer therapy method of employing a liposome entrapping cisplatin (column 18, claim 2) prepared by a method comprising the use of any suitable lipid known in the art that is capable of forming liposomal micelles, *e.g.*, DMPG, and of an organic solvent comprising an alcohol including ethanol, wherein the ratio of compound (cisplatin) to lipid used preferably ranges from about 1:1 to about 1:20 (column 5). Administration routes including intravenous administration for use in cancer therapy are also disclosed in column 6.

However, the Office admitted that Szoka does not teach explicitly a specific combination of a phosphatidyl glycerol lipid derivative and cisplatin, nor does Szoka teach the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles, nor does Szoka teaches the addition of a hydrophilic polymer/lipid complex as a stabilizer to the cisplatin micelles including the use of PEG-DSPE, PEG-DSPC, hyaluronic acid-DSPE, liposomes composed of cholesterol, HSPC and PEG-HSPC or PEG-DSPE.

The Office argued that however, at the time the invention was made, Perez-Soler et al. teach that a liposome made of cisplatin/DMPG is effective for use as a liposomal antitumor composition.

The Office stated that in addition, Abra et al. teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid derivatized with a hydrophilic polymer (PEG), and/or cholersterol, and/or HSPC is effective for

use to increase the stability of cisplatin during its *in vivo* delivery to a tumor site. The Office noted that in addition, the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles is allegedly taught.

The Office asserted that it therefore would have been obvious for one of ordinary skill in the art to have employed a liposome made of cisplatin/any known phosphatidyl glycerol lipid derivative as a liposomal antitumor composition. The Office also noted that one of ordinary skill in the art would have been motivated to have employed the liposome entrapping a cisplatin compound because Szoka teaches a cancer therapy method of employing a liposome entrapping cisplatin prepared by a method comprising the use of any suitable lipid known in the art that is capable of forming liposomal micelles, *e.g.*, DMPG, and of an organic solvent comprising an alcohol including ethanol, wherein the ratio of compound (cisplatin) to lipid used preferably ranges from about 1:1 to about 1:20, and because Perez-Soler et al. teach that a liposome made of cisplatin/DMPG is effective for use as a liposomal antitumor composition.

The Office also opined that it would have been obvious for one of ordinary skill in the art to have further employed a suitable lipid, *e.g.,* cholesterol, DSPE and/or HSPC, and a hydrophillic polymer as stabilizer to enhance the stability of the liposome of Szoka taken with Perez-Soler et al. The Office remarked that one of ordinary skill in the art would have been motivated to have employed the stabilizer complexes in the liposomes of the combined cited references because Abra et al. teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid derivatized with a hydrophilic polymer (PEG), and/or cholersterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery to a tumor site.

The Office maintained that it would also have been obvious as a matter of design choice for one of ordinary skill in the art to have employed the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles, particularly since it is common and routine in the prior art, as exemplified by Abra et al., for a skilled artisan to have employed the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles.

The Office concluded that thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Applicant respectfully traverses. Amended claim 1 and its dependents are directed to a method for producing cisplatin micelles by combining a suitable buffer solution, cisplatin and a negatively charged phosphatidyl glycerol lipid derivative in a molar ratio of 1:1 to 1:2 to form a cisplatin mixture. The mixture is then combined with an effective amount of at least a 30% ethanol solution to form a cisplatin mixture in its aqua form in micelles. Amended claim 2 and its dependents are directed to a method for producing cisplatin micelles by combining a suitable buffer solution, cisplatin and an effective amount of at least a 30% ethanol solution to form a cisplatin/ethanol solution. The solution is then combined with a negatively charged phosphatidyl glycerol lipid derivative in a molar ratio of 1:1 to 1:2 to form cisplatin in its aqua form in micelles.

Support for the amendments to claims 1 and 2 is found in the specification on page 3, lines 24 to 28; page 10, lines 29 to page 11, line 19; and page 32, lines 1 to 25.

As noted in the specification, Applicant's invention addresses and overcomes the prior art problem of low solubility of cisplatin and other positively charged drugs. Applicant's invention also overcomes the prior art problem of the toxicity of cisplatin and other drugs because enhanced solubility means that less drug is required and less likely to leak from the micelle before it reaches its target. (See Applicant's specification on page 3, lines 12 to 17).

Applicant's invention provides a method for obtaining cisplatin micelles, wherein the cisplatin is in its aqua form. Applicant notes that:

> "During steps A and B the initial powder suspension, which tends to give a precipitate of yellow cisplatin power, is converted into a gel (colloidal) form; during steps A and B <u>there is conversion of cisplatin to its aqua form</u> (by hydrolysis) of the chloride atoms and their replacement by water molecules bound to the platin) which is positively-charged and is the active form of cisplatin endowed with the antineoplastic activity; <u>the aqua cisplatin is simultaneous</u>

> complexed with the negatively-charged lipid into micelles in 30% ethanol. The cisplatin-DPPG electrostatic complex has already improved properties over free cisplatin in tumor eradication."

Emphasis added, page 32, lines 9 to 17 of Applicant's specification.

Szoka teaches away from the formation of aqueous cisplatin. Cisplatin is "dissolved" in an aprotic solvent such as DMSO (column 3, lines 5 to 8) which is then combined with a solubilizing amount of a lower alcohol or other aqueous solution. Szoka teaches that an aprotic solvents are ones that "are not hydrogen donors, and which do not include hydrocarbons or halogenated hydrocarbon solvent." (Emphasis added, column 4, lines 50 to 53). Thus, Szoka does not teach a means to provide cisplatin in its aqua form, since hydrolysis is avoided and water is not complexed to the cisplatin molecules. Moreover, Szoka teaches a method of encapsulation, not a method to produce a micelle by electrostatic attraction between the aqua cisplatin and the negatively charged lipid. The micelles of the invention may be used alone or can be encapsulated while retaining the aqua cisplatin in its biologically active form.

Perez - Soler also fails to teach or suggest a method to produce aqua cisplatin–micelle complexes. The compound sought to be encapsulated, *i.e.*, dichlorol (1, 2-diaminocyclo-hexane) platinum (II) rather than cisplatin to avoid the difficulties associated with the manufacture of cisplatin-drug compositions. The patentees produce an intermediate complex containing a halogen atom, which is then encapsulated. The conversion is necessary to overcome cisplatin's "low solubility in water and most organic solvents." (Column 1, lines 60 to 62 of Perez-Soler). Contrary to Applicant's invention, there is no suggestion of hydolysis of cisplatin.

Abra does not teach aqueous cisplatin in micelles. Rather, Abra teaches encapsulation or capture of the drug in a lipid bilayer. Abra does not rely on electrostatic interaction between the drug and the negatively charged lipid derivative to form a micelle.

Accordingly, the cited art, alone or in combination with each other, does not teach or suggest methods to produce cisplatin in its aqua form in a micelle, the micelles produced by the methods, or therapeutic methods using the micelles.

Claims 9, 13, 16, 17 and 19-21 stand rejected under 35 USC 103(a) as allegedly unpatentable over Szoka taken with Perez-Soler et al., Abra et al. and further in view of Unger et al. (US Pat. No. 6,028,066 ("Unger et al.)).

The Office remarked that to the extent that the combined cited references do not explicitly teach the use of hyaluronic acid - DSPE in the method, it would have been obvious for one of ordinary skilled in the art to have incorporated any glycosaminoglycan including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references, particularly glycosaminoglycan is routinely employed in the prior art to increase the stabilization and anti-thrombic properties of the lipid complexes. The Office also stated that one of ordinary skill in the art would have been motivated to have employed including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references because of the reasons set forth in the immediately preceding sentence and because Unger teaches that lipid complexed with hyaluronic acid can be used a stabilizer in any liposomal delivery composition.

The Office concluded that thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1, 2 and 5 also stand rejected under 35 USC 103(a) as allegedly unpatentable over Szoka taken with Perez-Soler et al., Abra et al., and further in view of Lee et al. (US Pat No. 5,908,777 ("Lee et al.").

The Office stated that the combined cited references of Szoka taken with Perez-Soler et al. and Abra et al. teach the encapsulation method of claims 1 and 2 as indicated above. The Office remarked that to the extent that the combined cited references do not teach explicitly the

use of a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution entrapped in the liposomal composition, the Office opined that Lee et al. teach that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex through cell membrane of a target cell, and that fusogenic peptide can be derivatived by adding a string of negatively-charged amino acids at the N or C-terminus of the peptide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution.

The Office concluded that it therefore would have been obvious for one of ordinary skill in the art to have further employed a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution.

The Office concluded that thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1, 2, 5 and 6 stand rejected under 35 USC 103(a) as allegedly unpatentable over Szoka taken with Perez-Soler et al., Abra et al., and further in view of Lee et al. and Gebeyehu et al. (US Pat. No. 5,334,761 ("Gebeyehu et al.").

The Office rejected claims 1, 2 and 5 as allegedly obvious over Szoka taken with Perez-Soler et al., Abra et al., and further in view of Lee et al. as applied, *supra*. To the extent that the combined cited references do not teach the use of a cationic lipid/DOPE complex as an additional fusogenic substance so as to enhance the transport of the cisplatin/lipid complex of the combined cited references, the office argued that Gebeyehu et al. is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell (entire document, abstract, column 1, column 4).

The Office concluded that therefore, it would have been obvious for one of ordinary skill in the art to have further employed any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex as taught by Szoka taken with Perez-Soler et al., Abra et al., and further in view of Lee et al.. The Office remarked that one of ordinary skill in the art would have been motivated to have added any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex because Gebeyehu et al. is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell, and because one would have expected that the addition of a fusogenic cationic lipid/DOPE complex would further generate an additive fusogenic effect so as to enhance the delivery of the cisplatin compound to target tumor cells.

Applicant respectfully traverses. As noted above, Szoka taken with Perez-Soler et al and Abra et al., neither teach nor suggest the micelles containing cisplatin in its aqua form, how to make the micelles or methods to use them. None of the secondary references cited by the Office (Unger et al. Lee et al., or Gebeyehu et al.) shore up the deficiencies in the disclosures of Szoka, Perez-Soler et al. and Abra et al., with respect to claims 1 and 2, from which all claims depend. Accordingly, the rejection of the claims as allegedly obvious in view of the art is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claim 22 stands rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The Office opined that Applicant's claimed invention encompasses a targeted therapy for targeting an effective amount of the encapsulated cisplatin of claims 16 and 17 to any solid tumor or metastasis. The Office stated that it is apparent that the encapsulated cisplatin of claims 16 and 17 does not even required to have any product and/or material so as to target the

encapsulated cisplatin to a desired tumor site. The Office argued that neither the prior art of record nor the as-filed specification teaches that the encapsulated cisplatin is capable of targeting only solid tumors or metastases.

Applicant respectfully traverses and directs the Office's attention to page 33 and Figures 2 to 4 wherein Applicant describes the results of the experiment showing targeted delivery. Accordingly, Applicant respectfully request removal of the rejection under 35 U.S.C. § 112, first paragraph.

Change in Agent's Address

The undersigned attorney would like to bring to the Office's attention a change of address. Please direct all future correspondence to the undersigned attorney at:

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III. CONCLUSION

No additional fee is deemed necessary in connection with the filing of this Amendment and Response. However, if the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-1189**, referencing no. **23896-7002**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Should a telephone advance prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 849-4950.

Respectfully submitted,

Date: February 14, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

DRAFT CLAIM AMENDMENTS

23962-7002

1. (Amended) A method for producing cisplatin micelles, comprising:

a) combining a suitable buffer solution, cisplatin and a negatively charged phosphatidyl glycerol lipid derivative in a molar ratio [range] of 1:1 to 1:2 to form a cisplatin mixture; and

b) combining the mixture of step a) with an effective amount of at least a 30% ethanol solution [to form cisplatin micelles], thereby producing a cisplatin mixture in its aqua form in micelles.

2. (Amended) A method for producing cisplatin micelles, comprising:

a) combining a suitable buffer solution, cisplatin with an effective amount of at least a 30% ethanol solution to form a cisplatin/ethanol solution; and

b) combining the solution with a negatively charged phosphatidyl glycerol lipid derivative in a [range] molar ratio of 1:1 to 1:2 [to form cisplatin micelles] thereby producing a cisplatin mixture in its aqua form in micelles.

5. (Amended) The method of claim 1 or 2, further comprising combining an effective amount of a free fusogenic peptide, a fusogenic peptide-lipid conjugate or a fusogenic peptide –PEG-HSPC conjugate to the mixture of step a) where the fusogenic peptide is derivatized with a stretch of 1-6 negatively-charged amino acids at the N or C- terminus and thus, able to bind electrostatically to [aquaplatin] the cisplatin mixture in its aqua form.

11. (Amended) The method of claim 10, wherein the lipid is selected from the group consisting of premade neutral liposomes, composed of cholesterol 10-60%, 40-90% hydrogenated soy phosphatidylcholine (HSPC) [40-90% and] 1-7% polyethyleucglycol (PEG)-HSPC [1-7% or lipids in solution, lipids in powder] and PEG-DSPE.

12. (Amended) The method of claim [10] 9 wherein the lipid comprises 10-60% cholesterol.

13. (Amended) A method for obtaining a cisplatin/lipid complex capable of evading macrophages and cells of the immune system when administered to a subject, the method comprising mixing an effective amount of the cisplatin micelles of claim [9] 10 with an effective amount of a lipid selected from the group consisting of PEG-DSPE, PEG-DSPC [or] and hyaluronic acid – DSPE.

16. (Amended) An encapsulated [Encapsulated] cisplatin obtainable by the method of claim 13.

17. (Amended) An encapsulated [Encapsulated] cisplatin obtainable by the method of claim 13.

18. (Amended) A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated cisplatin of claim [15] 16.

22. (Amended) A method for penetrating the cell membrane of a tumor cell [targeting solid tumors and metastases] in a subject comprising intravenous administration of an effective amount of the encapsulated cisplatin of claims 16 or 17.

23. (Amended) A method for penetrating the cell membrane of a tumor cell in a subject comprising administering an effective amount of the cisplatin micelle obtainable by the method of claim 7.

29 (New) The method of claim 9, wherein the vesicle – forming lipid is in solution or powder form.